Remarks

Claims 10, 11, and 13-19 are currently pending and stand rejected in this case. With this Reply, claim 12 is cancelled and claims 10, 11 and 13 are amended to more particularly point out and distinctly claim the invention. Amended claim 10 claims the use of a selective inhibitor of phosphodiesterase 1C. Applicant believes that the term "selective" is clear from the specification as a compound that inhibits some phosphodiesterases but not others. Additionally, support for the phosphodiesterase 1C inhibitors added in amended claim 13 is found on page 20, lines 4-10.

Rejections under 35 U.S.C. 112, first paragraph

Claims 10-19 stand rejected under 35 U.S.C. 112, first paragraph. It is asserted that the specification is enabled for administering an inhibitor of phosphodiesterase 1C to a mouse, but not for all mammals, including humans, by any means of administration (in particular oral administration). Applicant respectfully requests reconsideration and withdrawal of these rejections based on the following discussion.

As discussed in MPEP 2164.02, an *in vitro* or *in vivo* animal model in the specification constitutes a working example if that example correlates with the claimed method. The model is deemed to correlate if the model is recognized in the art as reasonably correlating to a specific condition. A rigorous or invariable exact correlation is not required. See also *In re Brana*, 34 USPQ2d 1436, 1441-1442 (Fed. Cir. 1995) and *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985).

In the present case, the PTO acknowledges that the specification is enabling for administration of at least some phosphodiesterase inhibitors to a mouse. Applicant asserts that the finding that the specification is enabling for administration of at least some phosphodiesterase inhibitors to a mouse establishes that the specification is

enabling for the full scope of the claims, including for any mammal including humans, any route of administration including oral, and any selective inhibitor of phosphodiesterase 1C.

With regard to the enablement for any mammal, including humans, applicant asserts that the TC3 cell model and the mouse model are established models for diabetes, such that results with those models would be expected to correlate with results in any diabetic mammal, including humans. These models are so well established that they represent standard *in vitro* and *in vivo* models that are used for research for human diabetes. See, e.g., the enclosed 10 abstracts for papers describing work performed before the priority date of the instant application, showing that the TC3 cell and the mouse model are accepted standards for diabetes research. The abstracts are: (TC3 cells): Fuhlendorff et al., Diabetes 47:345-51 (1998); Liang et al., Horm. Metab. Res. 29:255-60 (1997); Major et al., Diabetes 48:1372-80 (1999); Nagamatsu et al., Am. J. Physiol. Cell Physiol. 269:C480-6 (1995); Papas et al., Biochem. Biophys. Acta 1291:163-6 (1996); (*in vivo* mice): Beales et al., Diabetes Metab. Res. Rev. 15:21-8 (1999); Hoppener et al., Diabetologia 42:427-34 (1999); Ishikawa et al., Biol. Pharm. Bull. 21:928-33 (1998); Pieper et al., Proc. Natl. Acad. Sci. USA 96:3059-64 (1999); and Sreenan et al., Diabetes 47:1881-8 (1998). Since the use of TC3 cells and mice are established models for diabetes, applicant asserts that the skilled artisan would expect the claimed treatments to work with any mammal, including humans.

Regarding the route of administration, applicant notes that "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the

objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi & Horton*, 169 USPQ 367, 369 (CCPA, 1971)(emphasis in original). In the present case, the PTO merely states that the specification does not disclose the oral administration of the compounds. However, the PTO does not provide any reason to doubt that oral administration, or any other administration, would be effective. Indeed, the PTO provides examples of disclosures (under the 35 U.S.C. 102 rejections - Greenwald, and Truss et al.) where oral administration is disclosed. By stating that those disclosures anticipate the claimed invention, the PTO is tacitly stating that those disclosures are enabled for the claimed invention. Thus, the PTO, in citing Greenwald, and Truss et al. as prior art, is providing evidence that oral administration is enabled. At any rate, the PTO has not provided any reason to doubt the assertion that the claimed administration is enabled, as is required to maintain a rejection based on the lack of enablement of any particular administration route.

Regarding enablement for any selective inhibitor of phosphodiesterase 1C, applicant notes that the specification provides data that two selective inhibitors of phosphodiesterase 1C, 8MM-IBMX, and zaprinast, were effective in increasing glucose dependent insulin secretion, and inhibitors tested that did not inhibit phosphodiesterase 1C were not effective. Based on that data, the skilled artisan would believe that any selective inhibitor of phosphodiesterase 1C would be effective in the claimed methods. The PTO does not provide any specific reason to doubt that expectation. Additionally, whether any particular inhibitor is effective in the claimed method could be tested, without undue experimentation, using the methods described in the specification. This is all that is required to establish enablement for any selective inhibitor of phosphodiesterase 1C. See MPEP 2164.08(b) ("The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be

inoperative or operative with expenditure of no more effort than is normally required in the art."), citing *Atlas Powder Co. v. E.I. Du Pont De Nemours*, 224 USPQ 409, 414 (Fed. Cir. 1984).

The PTO, at page 4 of the Office Action, states that the prior art "suggests that the administration of the claim designated compositions to humans does not teach the claimed beneficial effect of insulin secretion. . . ." Applicant holds that this is not evidence that the claimed treatment is not enabled or believable, only that the claimed treatment is novel.

Applicant thus disagrees that the claimed invention is a "germ of an idea", since, as discussed above, the effectiveness of selective phosphodiesterase 1C inhibitors was established by standard models, and since the PTO cannot provide specific reasons why a skilled artisan would doubt the enablement of the claims. Additionally, with regard to the specific dosage required for any particular route of administration or selective phosphodiesterase 1C inhibitor, the specification establishes, at page 23, lines 3-17, that methods for establishing effective doses are routine and do not require undue experimentation.

In light of the above discussion, applicant respectfully requests withdrawal of the rejection of claims 10-19 under 35 U.S.C. 112, first paragraph.

Rejections under 35 U.S.C. 112, second paragraph

Claims 10-18 stand rejected under 35 U.S.C. 112, second paragraph as being indefinite for not being clear as to whether the claims encompass an *in vivo* and/or *ex vivo* administration of the inhibitor. Applicant notes that amended claim 10 requires that the inhibitor be administered to the mammal, and is therefore clear as to its scope. Applicant therefore requests withdrawal of this rejection.

Claim 11 also stands rejected under 35 U.S.C. 112, second paragraph as being unclear as to the scope of the derivative specified. Amended claim 11 clearly defines the specified compounds and isobutylmethylxanthines with only particular moieties as substitutions at positions 2 and 8. Applicant asserts that amended claim 11 is not indefinite. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 13 stands rejected under 35 U.S.C. 112, second paragraph as not providing the full name of IBMX. Applicant asserts that this rejection is moot because "IBMX" is no longer part of the claim.

Rejections under 35 U.S.C. 102(b)

Claims 10-14 and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Greenwald, U.S. Patent No. 5,521,191. Additionally, claims 10-13, 15, 16, and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Truss et al, WO97/05876. It is asserted that both references disclose the administration of a phosphodiesterase 1C inhibitor as claimed. Applicant respectfully requests reconsideration and withdrawal of these rejections in light of the claim amendments and the following discussion.

Claim 10 as amended requires that the phosphodiesterase IC inhibitor be administered to a mammal in need of increased glucose dependent insulin secretion. Neither Greenwald nor Truss et al. discloses the administration of a phosphodiesterase IC inhibitor to a mammal in need of increased glucose dependent insulin secretion. Therefore, neither of these references anticipate the claimed method. Accordingly, withdrawal of these rejections under 35 U.S.C. 102(b) is respectfully requested.

Rejections under 35 U.S.C. 103(a)

Claims 10-13 and 17-19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kohnert et al., 1982, Mol. Cell. Endocriol. 28:425-437, in view of Weiner et al., U.S. Patent No. 5,763,396, Bhagwart et al., U.S. Patent No. 6,056,977 and Bosies et al., U.S. Patent No. 4,017,539. Applicant respectfully requests reconsideration and withdrawal of these rejections in light of the claim amendments and the following discussion.

The claims as amended require, *inter alia*, the administration of a selective inhibitor of phosphodiesterase 1C to a mammal. None of the cited references teaches or suggests the administration of selective inhibitors of phosphodiesterase 1C. The phosphodiesterase 1C inhibitor described in Kohnert et al., IBMX, is not a selective inhibitor of phosphodiesterase 1C (see specification at page 29, line 21). In order to maintain a rejection under 35 U.S.C. 103(a), the cited reference(s) must, alone or in combination, teach or suggest every element of the rejected claims. Since none of the cited references teaches or suggests the use of a selective inhibitor of phosphodiesterase 1C, applicant asserts that this rejection cannot stand. Accordingly, applicant requests withdrawal of the rejections under 35 U.S.C. 103(a).

Conclusion

In light of the claim amendments and the above discussion, applicant respectfully requests withdrawal of all rejections and passage of the amended claims 10, 11, and 13-29 to allowance. If there are any minor matters preventing that result, applicant requests that Examiner Flood contact the undersigned attorney.

It is believed that the $55.00 extension of time fee is all that is required with this submission. However, if there are any unanticipated fees required to maintain pendency of this application, the PTO is authorized to withdraw those funds from Deposit Account 01-1785.

Respectfully submitted,

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Dated: New York, New York
December 3, 2003

By: _____
Elie H. Gendloff
Registration No.: 44,704

1: Diabetes. 1998 Mar;47(3):345-51. Related Articles, Link

Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes.

Fuhlendorff J, Rorsman P, Kofod H, Brand CL, Rolin B, MacKay P, Shymko R, Carr RD.

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The action of repaglinide, a novel insulin secretagogue, was compared with the sulfonylurea glibenclamide with regard to the hypoglycemic action in vivo, binding to betaTC-3 cells, insulin secretion from perifused mouse islets and capacity to stimulate exocytosis by direct interaction with the secretory machinery in single voltage-clamped mouse beta-cells. Two binding sites were identified: a high-affinity repaglinide (KD = 3.6 nmol/l) site having lower affinity for glibenclamide (14.4 nmol/l) and one high-affinity glibenclamide (25 nmol/l) site having lower affinity for repaglinide (550 nmol/l). In contrast to glibenclamide, repaglinide (in concentrations as high as 5 micromol/l) lacked the ability to enhance exocytosis in voltage-clamped beta-cells. Repaglinide was more potent than glibenclamide in stimulating insulin release from perifused mouse islets (EC50 29 vs. 80 nmol/l). The greater potency of repaglinide in vitro was paralleled by similar actions in vivo. The ED50 values for the hypoglycemic action were determined to be 10.4 and 15.6 microg/kg after intravenous and oral administration, respectively. The corresponding values for glibenclamide were 70.3 microg/kg (intravenous) and 203.2 microg/kg (oral). Further, repaglinide (1 mg/kg p.o.) was effective ($P < 0.001$) as an insulin-releasing agent in a rat model (low-dose streptozotocin) of type 2 diabetes. These observations suggest that the insulinotropic actions of repaglinide and glibenclamide in vitro and in vivo are secondary to their binding to the high-affinity repaglinide site and that the insulinotropic action of repaglinide involves botl distinct and common cellular mechanisms.

PMID: 9519738 [PubMed - indexed for MEDLINE]

1: Horm Metab Res. 1997 Jun;29(6):255-60. Related Articles, Link

GLUT1 is adequate for glucose uptake in GLUT2-deficient insulin-releasing beta-cells.

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The Department of Biochemistry and Biophysics and Diabetes Research Center, University of Pennsylvania School of Medicine, Philadelphia 19104-6015, USA.

GLUT2 may play an important role in pancreatic beta-cell glucose metabolism. A decrease in glucose uptake due to underexpression of GLUT2 has been considered as the cause of beta-cell dysfunction in diabetes with different pathogenesis. However, this view has been challenged by recent studies, in which the underexpression of GLUT2 was not accompanied by a decrease in glucose uptake. Our present aim is to evaluate the presumed importance of GLUT2 in maintaining the efficiency of beta-cell glucose uptake. We studied the kinetic characteristics of 3-O-methylglucose uptake in two beta-cell lines. One of these is the beta TC3 cell line which expresses GLUT1 and the other is the beta HC9 cell line which expresses both GLUT1 and GLUT2. Under equilibrium exchange conditions, 3-O-methylglucose transport in these two cell lines showed similar values of K(m) and V(max). The apparent IC50 of cytochalasin B for inhibiting 3-O-methylglucose transport in beta HC9 cells was nine times as high as in beta TC3 cells, indicating that GLUT1 is the critically important glucose transporter in the beta TC3 cell line and GLUT2 in the beta HC9 cell line. In both cell lines, th rates of glucose uptake were at least three times as fast as that of glucose phosphorylation. Our results suggest that GLUT1 is able to compensate for GLUT2 loss as it occurs in beta TC3 and maintains a commensurately high capacity of glucose uptake to sustain glucose metabolism in pancreatic beta-cells.

PMID: 9230344 [PubMed - indexed for MEDLINE]

1: Diabetes. 1999 Jul;48(7):1372-80. Related Articles, Link

Activation of the sphingomyelinase/ceramide signal transductio pathway in insulin-secreting beta-cells: role in cytokine-induced beta-cell death.

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Activation of the sphingomyelin/ceramide pathway may mediate interleukin-1-induced beta-cell death (Welsh, N: Interleuken-1beta-induced ceramide an diacylglycerol generation may lead to activation of the c-Jun NH2-terminal kinase and the transcription factor ATF-2 in the insulin-producing cell line RINm5F. J Biol Chem 271: 8307-8312, 1996). In this report, we have examined this pathway in more detail. Culture of beta-TC3 cells with 25 micromol/l ceramide analogs (N-acetyl- and N-hexanoylsphingosine) for 72 did not significantly affect glucose- and carbachol-induced insulin secretion. Dihydroceramide (N-acetyl- or N-hexanoylsphinganine), a structurally similar analog, had no effect on agonist-induced secretion. However, ceramide analogs both time- and dose-dependently decreased cell viability, while the dihydroceramide analog had no effect. The ceramide effect on cell viability mimicked the effect of the cytokines TNF-alpha, IL-1beta, and IFN-gamma, reported stimulators of sphingomyelin hydrolysis. Cytokines, however, failed to stimulate sphingomyelin metabolism. Furthermore, using two different methods to quantitate ceramide, cytokines failed to cause an increase in beta-cell ceramide content versus unstimulated or time-matched vehicle controls. Taken together, these data suggest that although ceramide analogs mimic the cytotoxic effect of cytokines, activation of the sphingomyelin/ceramide signaling pathway is not involved in cytokine-induced beta-cell death.

PMID: 10389841 [PubMed - indexed for MEDLINE]

Am J Physiol Cell Physiol 269: C480-C486, 1995;
0363-6143/95 $5.00

ARTICLES

Glucose transporter expression and functional role of hexokinase in insulin biosynthesis in mouse beta TC3 cells

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It was previously reported that insulin biosynthesis in mouse beta TC3 cells was regulated by glucose (Nagamatsu, S., and D. F. Steiner. Endocrinology 130: 748-754, 1992). In the present study, we examined the effect of glucose on the glucose transporter expression and hexokinase activities and determined the relationship between them and glucose-stimulated insulin biosynthesis in beta TC3 cells. Reverse transcriptase-polymerase chain reaction and Northern blot analysis revealed that beta TC3 cells expressed GLUT-1 and GLUT-3 glucose transporter mRNAs, but not GLUT-2. The levels of GLUT-1 and GLUT-3 mRNAs were not affected by glucose (0 or 11 mM glucose) over a period of 48 h. Immunoprecipitation of metabolically labeled beta TC3 cells with specific antibodies against GLUT-1 or GLUT-3 proteins revealed no effect of glucose on the biosynthesis of glucose transporters. Hexokinase [low Michaelis constant (Km) hexokinase] activity from cells incubated in 11 mM glucose for 48 h increased nearly twofold compared with cells maintained in 0 mM glucose, although the amount of cellular hexokinase protein detected by immunoblot analysis was unchanged between 0 and 11 mM glucose conditions. Glucokinase (high Km hexokinase) activity, in contrast, was not affected by glucose. Preincubation of beta TC3 cells with 2-deoxyglucose to inhibit hexokinase, thereby inhibiting all glycolysis, resulted in the decrease of glucose-stimulated insulin biosynthesis. Thus, in mouse beta TC3 cells that do not express GLUT-2, there is a close relationship between hexokinase activity and glucose-stimulated insulin biosynthesis, but not between the glucose transporter and glucose-stimulated insulin biosynthesis.

1: Biochim Biophys Acta. 1996 Oct 24;1291(2):163-6.

Effects of oxygen on metabolic and secretory activities of beta TC3 cells.

Papas KK, Long RC Jr, Constantinidis I, Sambanis A.

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We have investigated the rates of glucose consumption, lactate production and insulin secretion by mouse insulinoma beta TC3 cells exposed to high glucose and oxygen concentrations in the range of 132 mmHg (normoxia) to 0 mmHg (anoxia). The rates of glucose consumption and lactate production, and the yield of lactate on glucose were 6.4 +/- 0.2 nmol/h - 10(5) cells, 7.7 +/- 0.5 nmol/h - 10(5) cells, and 1.2 +/- 0.1 respectively, at oxygen concentrations between 132-25 mmHg. These values increased gradually as the oxygen concentration was reduced below 25 mmHg, reaching a maximur value of 12.8 +/- 0.4, 23.8 +/- 1.1, 1.9 +/- 0.1 respectively, at complete anoxia. Insulin secretion remained constant at 360 +/- 24 pmol/h - 10(8) cells at oxygen concentrations between 132-7 mmHg, but was inhibited at lower oxygen concentrations, dropping to 96 +/- 24 pmol/h - 10(8) cells at 0 mmHg The rate of insulin secretion in the presence of high glucose under anoxia wa significantly higher than the rate of basal secretion (28.2 +/- 3.0 pmol/h - 10 (8) cells) at normoxia. The secretory properties of beta TC3 cells at low oxygen concentrations may have implications in the development of a diffusion-based bioartificial tissue constructs for the long-term treatment of Insulin Dependent Diabetes Mellitus.

PMID: 8898878 [PubMed - indexed for MEDLINE]

1: Diabetes Metab Res Rev. 1999 Jan-Feb;15(1):21-8.

Diet can influence the ability of nicotinamide to prevent diabetes in the non-obese diabetic mouse: a preliminary study.

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BACKGROUND: The non-obese diabetic (NOD) mouse is a widely used model of Type 1 diabetes mellitus (Type 1 DM), which displays many of the characteristics of the disease found in humans. Nicotinamide (NA) is currently being tested in large-scale, multi-centre human trials for the prevention of Type 1 DM in subjects considered 'at risk' of developing the disease. Human trial populations will certainly differ in their dietary patterns and alterations were made to the diet given to NOD mice to determine if this could alter the effect of NA administration on Type 1 DM incidence. METHODS: The effect of NA in the diet was examined, both with and without carbohydrate in the form of a sucrose supplement, on diabetes incidence and insulitis levels in the NOD mouse. The effects of NA and sucrose were each tested alone as well as in combination. RESULTS: Diabetes was unaltered using a low dose NA-supplemented diet (625 mg/kg diet). Diabetes incidence was also unaltered using unmodified diet together with drinking water supplemented with either 5% or 10% w/v sucrose or plain water for controls. However, with mice given NA-supplemented diet (625 mg/kg diet) together with sucrose-supplemented or plain water as previously, diabetes was reduced in the NA+10% sucrose group ($p<0.001$). Finally, a higher dose of NA was given in supplemented diet (1000 mg/kg). Again, neither sucrose nor NA alone altered the incidence of diabetes, but NA treatment combined with a 10% w/v sucrose-supplemented drinking water reduced diabetes incidence ($p<0.001$). No mice showed alterations in insulitis, blood-glucose or insulin levels with respect to controls. CONCLUSION: Altering dietary patterns using sucrose can affect the ability of NA to prevent diabetes in the NOD mouse. This finding may be relevant for human studies with NA aimed at preventing Type 1 DM and suggests that diet may need to be monitored or even controlled in these studies.

1: Diabetologia. 1999 Apr;42(4):427-34.

Diabetologia

Extensive islet amyloid formation is induced by development of Type II diabetes mellitus and contributes to its progression: pathogenesis of diabetes in a mouse model.

Hoppener JW, Oosterwijk C, Nieuwenhuis MG, Posthuma G, Thijssen JH, Vroom TM, Ahren B, Lips CJ.

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AIMS/HYPOTHESIS: Type II (non-insulin-dependent) diabetes mellitus is a multifactorial disease in which pancreatic islet amyloid is a characteristic histopathological finding. Islet amyloid fibrils consist of the beta-cell protein "islet amyloid polypeptide" (IAPP)/"amylin". Unlike human IAPP (hIAPP), mouse IAPP cannot form amyloid. In previously generated transgenic mice, high expression of hIAPP as such did not induce islet amyloid formation. To further explore the potential diabetogenic role of amyloidogenic IAPP, we introduced a diabetogenic trait ("ob" mutation) in hIAPP transgenic mice. METHODS: Plasma concentrations of IAPP, insulin and glucose were determined at 3.5 (t1), 6 (t2), and 16-19 months of age (t3). At t3, the mice were killed and the pancreas was analysed (immuno)histochemically. RESULTS: In non-transgenic ob/ob mice, insulin resistance caused a compensatory increase in insulin production, normalizing the initial hyperglycaemia. In transgenic ob/ob mice, concurrent increase in hIAPP production resulted in extensive islet amyloid formation (more often and more extensive than in transgenic non-ob/ob mice), insulin insufficiency and persistent hyperglycaemia: At t3, plasma insulin levels in transgenic ob/ob mice with amyloid were fourfold lower than in non-transgenic ob/ob mice ($p < 0.05$), and plasma glucose concentrations in transgenic ob/ ob mice were almost twofold higher ($p < 0.05$). In addition, the degree of islet amyloid formation in ob/ob mice was positively correlated to the glucose:insulin ratio ($r(s) = 0.53$, $p < 0.05$). CONCLUSION/INTERPRETATION: Islet amyloid is a secondary diabetogenic factor which can be both a consequence of insulin resistance and a cause of insulin insufficiency. [Diabetol

PMID: 10230646 [PubMed - indexed for MEDLINE]

1: Biol Pharm Bull. 1998 Sep;21(9):928-33.

Actions of the novel oral antidiabetic agent HQL-975 in genetically obese diabetic db/db mice.

Ishikawa Y, Takagi Y, Takeno H, Watanabe K, Tani T.

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The hypoglycemic effect of the novel oral agent 3-[4-12-(5-methyl-2-phenyl oxazol-4-yl)-ethoxy]-phenyl]-2S-propyla mino-propionic acid (HQL-975) was examined in db/db mice with genetically obese non-insulin dependent diabetes mellitus (NIDDM). The oral administration of HQL-975 at 3.5 and 35.3 mg/kg/d for 7 d decreased the plasma glucose level of these mice in a dose-dependent manner. HQL-975 also significantly decreased the plasma triglyceride, total cholesterol, non-esterified fatty acid and insulin levels. In the oral glucose tolerance test, HQL-975-treated mice showed improved glucose tolerance and decreased endogenous insulin secretion. HQL-975 increased glycemic response to exogenous insulin in the mice. In the HQL-975-treated db/db mice adipocytes, the glucose uptake, insulin binding, and GLUT4 expression were increased compared with those in untreated db/db mice adipocytes. These results indicate that HQL-975 improved insulin action in db/db mice through receptor and post-receptor effects. In conclusion, HQL-975 is a new oral antidiabetic agent with a hypoglycemic effect which is associated with an insulin-sensitizing effect. This agent may therefore be effective for the treatment of NIDDM.

PMID: 9781841 [PubMed - indexed for MEDLINE]

1: Proc Natl Acad Sci U S A. 1999 Mar 16;96(6):3059-64. Related Articles, Link

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Poly(ADP-ribose) polymerase-deficient mice are protected from streptozotocin-induced diabetes.

Pieper AA, Brat DJ, Krug DK, Watkins CC, Gupta A, Blackshaw S, Verma A, Wang ZQ, Snyder SH.

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Streptozotocin (STZ) selectively destroys insulin-producing beta islet cells o the pancreas providing a model of type I diabetes. Poly(ADP-ribose) polymerase (PARP) is a nuclear enzyme whose overactivation by DNA strand breaks depletes its substrate NAD+ and then ATP, leading to cellular death from energy depletion. We demonstrate DNA damage and a major activation of PARP in pancreatic islets of STZ-treated mice. These mice display a 500% increase in blood glucose and major pancreatic islet damage. In mice with homozygous targeted deletion of PARP (PARP -/-), blood glucose and pancreatic islet structure are normal, indicating virtually total protection from STZ diabetes. Partial protection occurs in PARP +/- animals. Thus, PARP activation may participate in the pathophysiology of type I diabetes, for which PARP inhibitors might afford therapeutic benefit.

PMID: 10077636 [PubMed - indexed for MEDLINE]

1: Diabetes. 1998 Dec;47(12):1881-8.

Links

Adaptation to hyperglycemia enhances insulin secretion in glucokinase mutant mice.

Sreenan SK, Cockburn BN, Baldwin AC, Ostrega DM, Levisetti M, Grupe A, Bell GI, Stewart TA, Roe MW, Polonsky KS.

Department of Medicine, Howard Hughes Medical Institute, University of Chicago and Pritzker School of Medicine, Illinois 60637, USA.

The present study was undertaken to test the hypothesis that exposure to high glucose concentrations enhances insulin secretion in pancreatic islets from glucokinase-deficient mice. Insulin secretion and intracellular calcium ([Ca2+]i) were measured as the glucose concentration was increased from 2 to 26 mmol/l in islets from heterozygous glucokinase (GK)-deficient mice (GK+/-) and their wild-type littermates (GK+/+). Results obtained in islets incubated in 11.6 or 30 mmol/l glucose for 48-96 h were compared. GK+/- islets that had been incubated in 30 mmol/l glucose showed improved although not normal insulin secretory and [Ca2+]i responses to the standard glucose challenge as well as an enhanced ability to sense small amplitude glucose oscillations. These effects were associated with increased glucokinase activity and protein. In contrast, exposure of GK+/+ islets to 30 mmol/l glucose increased their basal insulin secretion but reduced their incremental secretory responses to glucose and their ability to detect small amplitude glucose oscillations. Thus exposure of GK+/- islets to 30 mmol/l glucose for 48-96 h enhanced their ability to sense and respond to a glucose stimulus, whereas similar exposure of GK+/+ islets induced evidence of beta-cell dysfunction. These findings provide a mechanistic framework for understanding why glucokinase diabetes results in mild hyperglycemia that tends not to increase over time. In addition, the absence of one allele of the glucokinase gene appears to protect against glucose-induced beta-cell dysfunction (glucose toxicity).

PMID: 9836519 [PubMed - indexed for MEDLINE]